Summary of Amendments to the Specification

The specification has been amended to correct the improper recitations of "*Borrellia Burgdorferi*"with *Borrelia burgdorferi*". In addition, Table VII has been amended to correct a typographical error. SEQ ID NOs: 57 and 58 were not used, and the polypeptide corresponding to SEQ ID NO: 67 in Table VII as originally filed was inadvertently labeled 78 instead of 68. Table VII has been amended to renumber SEQ ID NO: 78 to SEQ ID NO: 68 and then to renumber SEQ ID NOs: 59-86 SEQ I D NOs: 57-84. No new matte has been added.

Summary of Claim Amendments

Claims 1, 2, 8-11 have been amended to clarify that the *Borrelia* family is *Borrelia burgdorferi sensu stricto*. Support for this amendment is found in the specification at page 7, lines 7-8 and page 9, line 18 through page 10, line 17.

Claims 39 and 41 have been amended to state that OspC families are selected from the group consisting of: *Borrelia burgdorferi sensu stricto* OspC families A, B, I, and K, and *Borrelia afzelii* OspC families A and B. Support for this amendment is found in the specificaiton on page 14, line 26 through page 15, line 11.

Claim 43 has been amended to recite SEQ ID NOs: ending with SEQ ID NO: 84. Support for this amendment is found in Table VII and in the Sequence listing filed concurrently with the application.

Drawings

Formal Drawings are being filed concurrently herewith.

Objection to the Specification

The specification is objected to for improper recitation of *"Borrelia Burgdorferi."* The paragraphs containing the improper recitation have been replaced with paragraphs reciting *"Borrelia burgdorferi."*

Reconsideration and withdrawal of the objection are respectfully requested.

Rejection of Claims Under 35 U.S.C. § 112

Claims 1-13 and 39-43 are rejected under 35 U.S.C. § 112, first paragraph. The Examiner stated that the specification, while being enabling for protein compositions comprising *Borrelia burgdorferi sensu stricto* OspC proteins LipCB31, LipC12, UnlipC2, UnlipC2C7, UnlipC2C10, Unlip C2C12, UnlipC5C10, and UnlipC5C12, does not reasonably provide enablement for compositions comprising OspC from other *Borrelia*, or immunogenic fragments thereof.

Claims 1-13

Claim1 has been amended to clarify that the OspC families of subpart a) are from *Borrelia burgdorferi sensu stricto*. Claims 2 and 8-11 have been amended to agree with the amendment to Claim 1.

The specification provides enablement for compositions of OspC polypeptides or immunogenic fragments thereof from either at least two *Borrelia burgdorferi sensu stricto* OspC families selected from the group consisting of A, B, I, and K, or at least one OspC polypeptide or immunogenic fragment thereof from each of *Borrelia afzelii* OspC families A and B. The specification teaches the general principle that four families of *Borrelia burgdorferi sensu stricto* are responsible for disseminated disease in the human population, as defined by the *ospC* gene (page 31, line 8, through page 34, line 11). The specification provides exemplary members for each family and teaches the degree of homology in the *ospC* gene that defines each family (page 15, line 12, through page 16, line 3, Table II on page 29, and page 31, lines 8-18). In addition, the specification teaches the general principle that two families of *Borrelia afzelii* are responsible for disseminated disease in the human population, as represented by the *ospC* gene (page 34, lines 12-21). The specification provides exemplary members for each of these families and teaches the degree of homology in the *ospC* gene that defines each of these families (page 16, lines 4-11 and page 15, lines 12-15).

The specification demonstrates that eight different and specific examples of OspC compositions (LipCB31, LipC12, UnlipC2, UnlipC2C7, UnlipC2C10, Unlip C2C12, UnlipC5C10 and UnlipC5C12), are both antigenic (page 36, line 1 through page 40, line 3 and Figure 8) and immunogenic (page 40, line 4 through page 42, line 26). The specification teaches certain fragments of OspC and chimeric OspC polypeptides (page 16, line 12, through page 17,

line 25). The specification provides assays to test both the antigenicity of the OspC containing polypeptides of the present invention (page 36, line 5, through page 38, line 15) and the immunogenicity of the OspC polypeptides of the present invention (page 40, line 6, through page 42, lines 26 and Figures 2-7). The specification demonstrates the use of both assays for OspC compositions comprising whole OspC, fragments of OspC and chimeric OspC.

According to the specification, the eight specific OspC examples that demonstrate both antigenic and immunogenic properties represent the four *Borrelia burgdorferi sensu stricto* families, that are responsible for disseminated disease, and combinations of the four families. Each of the eight examples, without exception, are antigenic and immunogenic, as shown using the assays described in the specification, demonstrating the predictability of the claimed invention (Figures 2-8). The specification provides additional specific OspC compositions (Table VII, page 43) and teaches that other members of the four *Borrelia burgdorferi sensu stricto* families or other members of the two *Borrelia afzelii* families can be used in the OspC containing compositions of the present invention (page 15, line 12, through page 16, line 12).

The Examiner has given no reason to doubt the objective evidence of the specification. The Examiner has indicated that only a subset of the disclosed OspC proteins (LipCB31, LipC12, UnlipC2, UnlipC2C7, UnlipC2C10, Unlip C2C12, UnlipC5C10 and UnlipC5C12) are enabled by the specification. However, as described above, the specification has provided a general teaching that four families of *Borrelia burgdorferi sensu stricto* and two families of *Borrelia afzelii* are responsible for disseminated human disease. The specification provides eight examples of OspC containing compositions, including whole OspC (LipCB31 and LipC12), fragments of OspC (UnlipC2) and chimeric OspC comprising two or more fragments (UnlipC2C7, UnlipC2C10, Unlip C2C12, UnlipC5C10 and UnlipC5C12), each of which are demonstrated to be both antigenic and immunogenic. Given the eight proven examples and the description of the relevant families of *Borrelia burgdorferi sensu stricto* and *Borrelia afzelii*, the description of useful OspC fragments, and the assays for antigenicity and immunogenicity provided in the specification, one of ordinary skill in the art can make and use the claimed invention without undue experimentation.

Claims 39-42

Claims 39 and 41 have been amended to recite "wherein said OspC families are selected from the group consisting of: *Borrelia burgdorferi sensu stricto* OspC families A, B, I, and K, and *Borrelia afzelii* families A and B."

The chimeric proteins of Claims 39-42 are enabled because based on the teachings provided in the specification, one of ordinary skill in the art would know how and be able to produce the chimeric OspC of the present invention without undue experimentation. The specification provides the sequences of both lipidated and unlipidated OspC (see for example, Table V, page 39) and teaches that at least 22 *ospC* sequences are available in GenBank. The specification teaches chimeric OspC proteins comprising two or more polypeptides as claimed in Claims 39-42 (see page 17, lines 1-25; and page 36, line 1 through page 44, line 2). According to the specification, the nucleotide numbering is based on the OspC sequence from B31, as numbered in GenBank accession number U01894, wherein base one is in the start codon (page 25, lines 21-23). The specification provides the DNA and protein sequences of several OspC chimeric proteins as presently claimed (see for example, Table V, page 39). Using the teachings of the present invention regarding which OspC family members and which portion of said OspC family members to use, one of ordinary skill in the art can make and use the OspC chimeras of the present invention using no more than routine molecular biology techniques.

Claim 43

Claim 43 is drawn to specific OspC proteins selected from the indicated SEQ ID NOs. As noted by the Examiner, the specification is enabled for several compositions including LipCB31 (SEQ ID NO: 44), LipC12 (SEQ ID NO: 22), UnlipC2 (SEQ ID NO: 8), UnlipC2C7 (SEQ ID NO: 32), UnlipC2C10 (SEQ ID NO: 34), Unlip C2C12 (SEQ ID NO: 36), UnlipC5C10 (SEQ ID NO: 40) and UnlipC5C12 (SEQ ID NO: 42). As described above, all five chimeric OspC tested demonstrated antigenic and immunogenic properties. Based on the specification and the working examples, one of ordinary skill in the art can make and use the sequences of Claim 43 without undue experimentation.

Therefore, Claims 1-13 and 39-43 are enabled under 35 U.S.C. § 112, first paragraph. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims Under 35 U.S.C. §112, Second Paragraph

Claim 2 has been rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. In particular, the Examiner stated that Claim 2 is drawn to one or more OspC polypeptide from each family, but that it is unclear if the claim means that each family has more than one OspC.

Applicants respectfully disagree that the claim is indefinite. However, solely to expedite prosecution, Claim 2 has been amended to recite "each *Borrelia burgdorferi sensu stricto* family of the group of subpart a)." Claim 1, subpart a) recites that the composition comprises one or more OspC polypeptides or immunogenic fragments thereof from at least two *Borrelia burgdorferi sensu stricto* families selected from the group consisting of A, B, I, and K. Claim 2 recites that the composition comprises one or more OspC polypeptide or fragment thereof from each family of the group of Claim 1, subpart a). The fact that each family includes several members fails to render Claim 2 indefinite because it is clear that Claim 2 requires at least one polypeptide from each family of Claim 1, subpart a).

Claim 43 has been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject-matter which Applicants regards as the invention. In particular, the Examiner points out that neither SEQ ID NO: 58 nor SEQ ID NO: 68 appear to be mentioned in the specification.

Applicants thank the Examiner for the thorough examination of the specification. The specification has been amended to correct obvious errors. SEQ ID NOs: 57 and 58 were not used, and the polypeptide corresponding to SEQ ID NO: 67 in Table VII as originally filed was inadvertently labeled 78 instead of 68. Therefore, Table VII on page 43 has been amended to change 59 to 57 and 60 to 58. The subsequent numbers have been adjusted down by 2, accordingly. In addition, the second 78 has been changed to 66. This amendment puts the sequence numbering in the specification into agreement with the numbering provided in the sequence listing which was filed concurrently with the application. No new matter has been added.

Claims 2 and 43 meet the requirements of 35 U.S.C. § 112, second paragraph, reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Sandra A Brockman

Sandra A. Brockman
Registration No. 44,045
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133
Dated: 9-26-02

MARKED UP VERSION OF AMENDMENTS

Specification Amendments Under 37 C.F.R § 1.121(b)(1)(iii)

The paragraph at page 1, line 13 through page 2, line 16 is being replaced with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Lyme disease begins at the site of a tick bite, producing a primary infection with spread of the organism to secondary sites occurring early in the course of infection. Lyme disease is a progressive multi-system disorder and is the most common vector-borne disease in both North America and Europe. This disease was first described as a focus of pediatric arthritis patients in Old Lyme, CT (Steere, A.C., *et al., Arth. Rheum.,* 20:17 (1977)). The association of this syndrome with the bite of the deer tick, *Ixodes scapularis*, led to the identification of the spirochete *Borrelia burgdorferi* as the causative agent (Burgdorfer, W., *et al., Science,* 216:1317-1319 (1982)). As culture isolation of the bacterium from clinical and field samples became more efficient, Baranton and colleagues described three pathogenic genospecies, *B.* [*Burgdorferi*] *burgdorferi sensu stricto* (*B.* [*Burgdorferi*] *burgdorferi* or *B.b.s.s.*), *B. afzelii*, and *B. garinii* (Baraton, G., *et al., Int. J. Syst. Bacteriol.,* 42:378-383 (1992)). These are members of a species complex, *B. burgdorferi* sensu lato, which consists of at least 10 different genospecies (Piken, R.N., *et al., J. Invest. Dermatol.,* 110:211-214 (1998); Postic, D., *et al., Int. J. Syst. Bacteriol.*, 44:743-752 (1994); Valsangiacomo, C.T., *et al., Int. J. Syst. Bacteriol.*, 47:1-10 (1997)). *B.* [*Burgdorferi*] *burgdorferi*, *B. afzelii* and *B. garinii* are thought to be pathogenic and all are found in Europe, but in North America, *B. burgdorferi* is the only pathogenic genospecies found. Each of these three genospecies is associated with distinct clinical manifestations (Van Dam, A. P. *et al., Clin. Infect. Dis.,* 17:708-717 (1993)). This implies that differences in genospecies may play an important role in the wide array of clinical manifestations observed in Lyme Disease.

The paragraph at page 10, lines 18-26 is being replaced with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

There is evidence that *ospC* has been transferred between strains and even between genospecies (Wang I-N, *et al., Genetics, 151*:15-30 (1998)). This is not true of *Borrelia* chromosomal genes (Dykhuizen, D.E., *et al., Proc. Natl. Acad. Sci.*, 30:10163-10167 (1999); Maynard Smith, J. and Smith, N.H., *Mol. Biol. Evol.*, 15:590-599 (1998)). However, *ospA* and *ospC* alleles in *B.* [*Burgdorferi*] *burgdorferi* sensu stricto are almost completely linked (Wang I-N, *et al., Genetics,* 151:15-30 (1999)). This suggests that once an *ospC* allele has been transferred into a particular background, there is little or no selection for another similar recombination event. Thus, each major *ospC* group represents a clonal population descended from a single recombination.

The paragraph at page 43, lines 1-25 is being replaced with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

TABLE VII

OspC Polypeptides and Chimeric Polypeptides of the Present Invention

POLYPEPTIDE	SEQ ID NO.:(DNA)	(POLYPEPTIDES)
[1]unlip OspC kkp(55-621*)	45	46
unlip OspC PKO	47	48
unlip OspC TRO	49	50
[2]unlip OspC-55B31/ 58PKO/56TRO	51	52
unlip OspC1-TRO	53	54
unlip OspC-TRO	55	56
[3]Blip OspC1C10	[59] 57	[60] 58
BlipOspC12	[61] 59	[62] 60
Blip OspC1-TR0	[77] 75	[78] 76
Blip OspC2C7	[67] 65	[78] 66
Blip OspC2C10	[63] 61	[64] 62

Blip OspC2C12	[65] 63	[66] 64
Blip OspC2-TRO	[69] 67	[70] 68
Blip OspC5C7	[75] 73	[76] 74
Blip OspC5C10	[71] 69	[72] 70
Blip OspC5C12	[73] 71	[74] 72
Blip OspCB31C10	[79] 77	[80] 78
Blip OspCB31C12	[81] 79	[82] 80
Blip OspCPkoTro	[83] 81	[84] 82
Blip OspC-55B31/58Pko/56Tro	[85] 83	[86] 84

Claim Amendments Under 37 C.F.R § 1.121(c)(1)(ii)

1. (Amended) A composition comprising OspC polypeptides from Lyme Disease causing *Borrelia* wherein either:

   a) said composition comprises one or more OspC polypeptides or immunogenic fragments thereof from at least two *Borrelia burgdorferi* sensu stricto OspC families selected from the group consisting of: A, B, I, and K, excepting the combination consisting of two OspC proteins wherein one OspC protein is from family A and the second OspC protein is from family I, or;

   b) said composition comprises at least one OspC polypeptide or immunogenic fragment thereof from each of *Borrelia afzelii* OspC families A and B.

2. (Amended) The composition of Claim 1 comprising one or more OspC polypeptides or fragments thereof from each [of] *Borrelia burgdorferi* sensu stricto [families] family of the group of subpart a).

8. (Amended) The composition of Claim 7, wherein *Borrelia burgdorferi* sensu stricto OspC family A comprises strains B31, CA4, HII, IPI, IP2, IP3, L5, PIF, Pka, Txgw and strains containing *ospC* allele OC1.

9. (Amended) The composition of Claim 7, wherein *Borrelia burgdorferi* sensu stricto OspC family B comprises strains 35B808, 61 BV3, BUR, DK7, PB3, Z57 and strains containing *ospC* genes OC2 and OC3.

10. (Amended) The composition of Claim 7, wherein *Borrelia burgdorferi* sensu stricto OspC family I comprises strains 297, HB19 and strains containing *ospC* gene OC10, wherein strain 297 is characterized by *ospC* of GenBank accession number L42893.

11. (Amended) The composition of Claim 7, wherein *Borrelia burgdorferi* sensu stricto OspC family K comprises strains 272, 297, 28354, KIPP, MUL and strains containing *ospC* gene OC12 and OC13, wherein strain 297 is characterized by *ospC* of GenBank accession number U08284.

39. (Amended) A chimeric protein comprising OspC polypeptides from two or more Lyme Disease causing OspC families of Lyme Disease causing *Borrelia* wherein said chimeric protein comprises:

a) a first OspC polypeptide encoded by a nucleic acid comprising a sequence from about nucleotide 26 to about nucleotide 621 of an *ospC* gene from a first OspC family and

b) a second OspC polypeptide encoded by a nucleic acid comprising a sequence from about nucleotide 28 to about nucleotide 570 of an *ospC* gene from a second OspC family,

wherein said OspC families are selected from the group consisting of: *Borrelia burgdorferi sensu stricto* OspC families A, B, I, and K, and *Borrelia afzelii* OspC families A and B.

41. (Amended) A chimeric protein comprising OspC polypeptides from two or more Lyme Disease causing OspC families of Lyme Disease causing *Borrelia* wherein said chimeric protein comprises:

a) a first OspC polypeptide encoded by a nucleic acid comprising a sequence from about nucleotide 53 to about nucleotide 570 of an *ospC* gene from a first OspC family and

b) a second OspC polypeptide encoded by a nucleic acid comprising a sequence from about nucleotide 28 to about nucleotide 570 of an *ospC* gene from a second OspC family,

wherein said OspC families are selected from the group consisting of: *Borrelia burgdorferi sensu stricto* OspC families A, B, I, and K, and *Borrelia afzelii* OspC families A and B.

43. (Amended) A chimeric OspC protein selected from the group consisting of: SEQ Id Nos: 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, and 84 [and 86].